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Outcomes after abdominal aortic aneurysm repair requiring a suprarenal cross-clamp

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Objective: **The objective of this study was to analyze the early and late outcomes of patients who require a suprarenal aortic cross-clamp during elective open repair of an abdominal aortic aneurysm (AAA).**
Methods: **Patients from 1998 to 2012 who required a suprarenal aortic cross-clamp during elective open AAA repair were reviewed. Data abstracted included demographics and comorbidities; preoperative, perioperative, and late renal function; late interventions related to AAA repair; and late mortality. A decrease in renal function was defined as a >30% decline in estimated glomerular filtration rate (eGFR) compared with the preoperative value. Primary outcomes included renal function, intervention-free survival, and overall survival.**
Results: **During the study period, 211 patients underwent open elective or urgent AAA repair; 69 required a suprarenal cross-clamp. The mean age was 71 years, and 80% were men. The mean preoperative creatinine concentration was 1.2 mg/dL, and the mean preoperative eGFR was 66 mL/min/1.73 m^2. Location of the aortic cross-clamp was suprarenal (37), supramesenteric (21), and supraceliac (11). Perioperatively, 21 patients (30%) experienced a significant decrease in eGFR; four patients required hemodialysis. Six patients had full recovery of renal function by discharge. Perioperative morbidity and mortality were 35% and 4%, respectively. At a mean follow-up of 3 years, seven patients had an eGFR significantly less than the preoperative value. Late interventions related to the AAA repair were required in eight patients. Indications included wound complication (3), anastomotic aneurysm (2), incisional hernia (1), anastomotic graft stenosis (1), and proximal aortic dilation (1). Overall 5-year intervention-free survival was 62% and overall survival 77%. Intervention-free survival was enhanced by antiplatelet use ($P = .04$), whereas overall survival was decreased by chronic obstructive pulmonary disease ($P = .003$) and perioperative pneumonia ($P = .001$).**
Conclusions: **More than a quarter of patients requiring a suprarenal cross-clamp during open AAA repair experience renal dysfunction. Late graft-related complications are few, with preoperative and perioperative pulmonary function negatively affecting overall patient survival. (J Vasc Surg 2014;60:893-9.)**

Patients with a juxtarenal or suprarenal abdominal aortic aneurysm (AAA) represent a small percentage of all patients with aortic aneurysms. Previous studies evaluating open repair of juxtarenal and suprarenal AAAs show perioperative mortality rates that range from 1% to 12% as well as a significant incidence of postoperative renal dysfunction.[1-4] In particular, renal dysfunction can occur in 15% to 40% of patients requiring a suprarenal cross-clamp and is often the predominant morbidity.[2,4-6]

Fenestrated endovascular aneurysm repair (f-EVAR) is an endovascular alternative to open juxtarenal and suprarenal AAA repair. Experience to date, predominantly from Europe, has demonstrated 30-day mortality rates of <1% to 4% and 3-year survival of up to 89%. However, early and late renal dysfunction is a concern, with a 10% target vessel loss in the early postoperative period and up to a 25% incidence of late renal dysfunction.[7-13]

This report reviews our recent institutional experience with open juxtarenal and suprarenal AAA repairs with a focus on early and late renal dysfunction as well as intervention-free and overall survival. Our objective was to determine the results of these challenging repairs in the endovascular era and to provide late-term information on renal dysfunction and survival. Such information provides a context for future therapeutic decisions concerning open vs endovascular approaches to juxtarenal and suprarenal AAAs.

METHODS

A retrospective review of all patients who underwent open AAA repair at the Keck Hospital of University of Southern California from August 1998 to June 2012 was performed. The review was approved by the University of Southern California Institutional Review Board. Patient consent was not required. Only patients who required a suprarenal aortic cross-clamp for urgent or elective AAA repair were included. Ruptured AAAs were excluded.

Demographics including age, race/ethnicity, sex, and smoking status were abstracted. Comorbidities included diabetes, hypertension, dyslipidemia, coronary artery disease, cerebrovascular disease, and chronic obstructive pulmonary disease. Use of preoperative antiplatelet and

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Table I. Baseline characteristics and comorbidities of patients

	N = 69
Age, years	71 ± 8
Preoperative creatinine level, mg/dL	1.2 ± 0.67
Preoperative eGFR, mL/min/1.73 m^2	66 ± 22
Aneurysm size, cm	6.12 ± 1.5
Sex	
Male	55 (79.7)
Female	14 (20.3)
Hypertension	61 (88.4)
Diabetes	15 (22.1)
Hyperlipidemia	47 (68.2)
Statin	52 (75.4)
Coronary artery disease	30 (43.5)
Previous CABG	15 (21.7)
Previous PTCA	8 (11.6)
Antiplatelet	36 (56.3)
Aspirin	33 (47.8)
Clopidogrel	1 (1.5)
Aspirin and clopidogrel	4 (5.8)
Smoking history	58 (84.1)
Recent[a]	32 (46.4)
Previous[b]	26 (37.7)
Hemodialysis	1 (1.5)
Cerebrovascular disease	9 (13.1)
TIA	4 (5.8)
CVA	5 (7.3)
COPD	12 (17.7)
Untreated	6 (8.8)
Receiving medications	5 (7.4)
Home oxygen therapy	1 (1.5)
Symptomatic aneurysm	8 (11.6)

CABG, Coronary artery bypass graft; *COPD,* chronic obstructive pulmonary disease; *CVA,* history of stroke (cerebrovascular accident); *eGFR,* estimated glomerular filtration rate; *PTCA,* percutaneous coronary angioplasty or stent; *SD,* standard deviation; *TIA,* history of transient ischemic attack.

Continuous data are presented as mean ± standard deviation and categorical data as number (%).

[a]Current smoker or quit <1 year ago.

[b]Quit smoking >1 year ago.

statin, previous aortic or cardiac surgery, and presence of symptoms related to the aneurysm were recorded. Renal function was assessed by serum creatinine (sCr) concentration and estimated glomerular filtration rate (eGFR) with the Modification of Diet in Renal Disease (MDRD) formula. Renal dysfunction was defined as sCr concentration >1.5 mg/dL or eGFR <60 mL/min/1.73 m^2. Recorded operative details included retroperitoneal vs transperitoneal approach; location of proximal aortic anastomosis; location of cross-clamp relative to renal, superior mesenteric, and celiac arteries; use of bypass grafts and vessel reimplantation; lowest intraoperative systolic blood pressure; estimated blood loss; and blood transfusion requirements. Perioperative outcomes were defined as events occurring within 30 days of the operation or during the original hospital stay if it was longer than 30 days. Perioperative mortality and morbidity, including myocardial infarction, pneumonia, arrhythmia, stroke, need for hemodialysis, paraplegia, bowel ischemia, wound infection, and unplanned return to the operating room, were tabulated.

Primary outcome measures were early and late renal function, intervention-free survival, and overall survival. A decrease in renal function was defined as a >30% decline in eGFR compared with the preoperative value. Late interventions were defined as any procedure or operative intervention required as a direct result of the original operation, including incisional hernia and need for anastomotic revision of the open repair. Statistical analysis was performed with the SAS 9.2 software (SAS Institute Inc, Cary, NC). Summary results for continuous variables are reported as mean ± standard deviation and as frequency (percentage) for categorical variables. Wilcoxon rank sum test was used to assess continuous variables, and χ^2 or Fisher exact test was used for categorical variables. Intervention-free survival and overall survival were calculated by the life-table method as outlined by the Society for Vascular Surgery Ad Hoc Committee on Reporting Standards. Univariate analysis was performed to determine factors that were significantly associated with intervention-free and overall survival. Multivariate Cox proportional hazards models were created, if indicated, to assess the association of variables found significant on univariate analysis. A value of $P < .05$ was considered significant.

RESULTS

During the study period, 211 patients underwent open AAA repair. Of this cohort, 69 (33%) required a suprarenal cross-clamp. The mean age of the patients was 71 years, and 80% of the patients were men (Table I). The majority were taking a statin (75%), had hypertension (88%), and had a smoking history (84%). The mean aneurysm size was 6.12 ± 1.5 cm. Twelve percent of patients had symptomatic aneurysms and required urgent repair within 24 hours of admission. Mean preoperative sCr concentration and mean preoperative eGFR were 1.2 (0.6-5.6) mg/dL and 66 (10-118) mL/min/1.73 m^2, respectively. Five patients had sCr concentration >1.5 mg/dL, whereas 23 had eGFR <60 mL/min/1.73 m^2.

All aortic repairs were performed with an anatomically placed Dacron graft. The operative approach was retroperitoneal in 70%; the location of the aortic cross-clamp was suprarenal in 54%, supramesenteric in 30%, and supraceliac in 16%. Fourteen patients had suprarenal aneurysms; the remainder were juxtarenal. For juxtarenal AAAs, proximal aortic anastomoses were performed with the suture line incorporating the lower margin of the renal artery origin. Aneurysms involving renal/visceral vessels were repaired by various combinations of beveled anastomoses, vessel reimplantation, and bypass. Renal/visceral reimplantation was performed in 16 patients (23%), and visceral/renal artery bypass was performed in six patients (9%). No specific renal cooling measures were used during the suprarenal cross-clamping. Mean operative time was 314 minutes; median operative time was 294 minutes (range, 132-629 minutes).

Mean length of stay was 9 days, with a range of 3 to 41 days. Morbidity occurred in 24 patients (35%) and is listed in Table II. Six patients required a return to the operating room for one of the following: lower extremity

Table II. Perioperative morbidity

	N = 69, No. (%)
Cerebrovascular	0
Paraplegia	1 (1.5)
Myocardial infarction	1 (1.5)
Renal dysfunction	21 (30.4)
Transient insufficiency	17 (24.6)
Hemodialysis	4 (5.8)
Perioperative arrhythmia	3 (4.3)
Bowel ischemia requiring resection	2 (2.9)
Return to operating room	8 (11.6)
Pneumonia treatment	7 (10.1)
Wound complications	1 (1.5)
In-hospital mortality	3 (4.35)

ischemia, renal ischemia, unexplained acidosis, fascial dehiscence, or bleeding. Seven patients required treatment for pneumonia, which was diagnosed by sputum culture and confirmed by positive findings on chest imaging.

Perioperatively, 21 patients (30%) experienced a significant decline in renal function. Four patients required hemodialysis. Three of the four patients requiring hemodialysis died in the hospital; in one patient, hemodialysis was no longer required at time of discharge. Of the 17 patients with a 30% decline in the eGFR, renal function had returned to baseline in six by the time of discharge. Mean discharge sCr concentration was 1.33 (0.4-6.8) mg/dL, and eGFR was 67 (8-211) mL/min/1.73 m^2. The only perioperative factors significantly associated with renal dysfunction were operative time longer than 4 hours ($P = .03$) and pneumonia ($P = .04$), although requirement of blood transfusion approached significance (Table III). Preoperative sCr concentration >1.5 mg/dL or eGFR <60 mL/min/1.73 m^2 was not predictive of postoperative decline in renal function ($P = .6$).

Three patients died, for a perioperative mortality of 4%. One patient developed lower extremity and bowel ischemia resulting in multisystem organ failure. A second patient with known ischemic cardiomyopathy had a perioperative myocardial infarction resulting in sustained ventricular tachycardia and death. A third patient developed hemodynamic instability and multisystem organ failure in the postoperative period. The patient's family opted to withdraw care. All three patients required hemodialysis postoperatively.

At a mean follow-up of 3.3 years, reinterventions were required in eight patients (12%). Indications included wound complication (3), anastomotic aneurysm/stenosis (3), incisional hernia (1), and proximal aortic dilation (1). There were 19 (28%) late deaths, none of which was directly related to the initial operation.

Forty patients had a documented sCr concentration and calculated eGFR at follow-up. Seven patients (17.5%) had a 30% or greater decrease compared with their preoperative value, with one patient progressing to hemodialysis. All seven patients had experienced a perioperative decline in eGFR of >30%. Whereas preoperative sCr concentration and eGFR were not associated with decrease in eGFR at follow-up, both discharge sCr concentration >1.5 mg/dL ($P = .013$) and discharge eGFR <60 mL/min/1.73 m^2 ($P = .022$) were associated with a late decline in renal function (Table IV).

Table III. Univariate analysis of factors affecting perioperative renal function

	P *value*
Age	.66
Hypertension	.19
Diabetes	.08
Hyperlipidemia	1
CAD	.55
Preoperative sCr level	.8
Preoperative eGFR	.6
Statin	.5
Antiplatelet	1
Smoker, current or previous	1
Cerebrovascular disease	.67
COPD	.72
Transperitoneal approach	.26
Retroperitoneal approach	.26
Aneurysm location[a]	.53
Concomitant renal artery intervention[b]	.08
Suprarenal cross-clamp	.18
Supramesenteric cross-clamp	.5
Operative time >4 hours	.03
Hypotension	
Systolic BP <100 mm Hg	.75
Systolic BP <80 mm Hg	.33
Estimated blood loss	
>1 L	.76
>2 L	.11
Transfusion	.06
Perioperative pneumonia	.04
Perioperative arrhythmia	.27
Return to operating room	.44

BP, Blood pressure; *CAD*, coronary artery disease, current or history; *COPD*, chronic obstructive pulmonary disease; *eGFR*, estimated glomerular filtration rate.
[a]Juxtarenal vs suprarenal.
[b]Renal artery bypass, reimplantation.

The 5-year intervention-free survival was 62% (Fig 1). Intervention-free survival was enhanced by antiplatelet use ($P = .04$). Prior aortic surgery ($P = .06$) and new-onset arrhythmia ($P = .06$) approached significance for negatively affecting intervention-free survival; but on multivariate analysis, only antiplatelet use remained significant ($P < .05$; Table V). Overall 5-year survival and 10-year survival were 77% and 52%, respectively (Fig 2). On univariate analysis, survival was decreased by a history of pulmonary disease ($P = .003$) and perioperative pneumonia ($P = .001$), both of which remained significant on multivariate analysis (Table VI). Preoperative renal dysfunction and postoperative decline in renal function were not significantly associated with intervention-free or overall survival.

DISCUSSION

Open repair of a juxtarenal or suprarenal AAA requires the placement of a suprarenal cross-clamp. Warm renal ischemia time during cross-clamping affects renal function,

Table IV. Univariate analysis of factors affecting long-term renal function

	P *value*
Age	.99
Hypertension	1
Diabetes	.23
Hyperlipidemia	.66
CAD	.22
Preoperative eGFR	.73
Statin	.64
Antiplatelet	.43
Smoker, current or previous	.28
Cerebrovascular disease	.66
COPD	.56
Transperitoneal approach	.18
Retroperitoneal approach	.94
Aneurysm location[a]	1
Concomitant renal artery intervention[b]	.39
Operative time > 4 hours	.65
Hypotension	
Systolic BP <100 mm Hg	1
Systolic BP <80 mm Hg	.49
Estimated blood loss	
>1 L	1
>2 L	1
Transfusion	.39
Perioperative pneumonia	7.2
Perioperative renal dysfunction	<.0001
Discharge sCr level, >1.5 mg/dL	.01
Discharge eGFR, <60 mL/min/1.73 m^2	.02
Perioperative arrhythmia	1
Return to operating room	.33

BP, Blood pressure; *CAD,* coronary artery disease, current or history; *COPD,* chronic obstructive pulmonary disease; *eGFR,* estimated glomerular filtration rate.
[a]Juxtarenal vs suprarenal.
[b]Renal artery bypass, reimplantation.

which is the major source of postoperative morbidity and has, in some reported experiences, a negative impact on patient survival—both early and late. The impact of a suprarenal cross-clamp on renal function has been quantified by Marrocco-Trischitta et al.[14] They reported a median late decrease in eGFR by 31.6% for patients with suprarenal cross-clamping compared with a median 6.5% decrease with infrarenal cross-clamping. Tsai et al[15] reported a 5-year survival of 74% and found that postoperative renal dysfunction after suprarenal cross-clamping had a negative impact on survival (relative risk, 1.73; $P = .02$). The adverse consequences of a suprarenal cross-clamp on renal function and survival are currently of interest, given advances in endovascular technology, which in essence eliminates the need for a suprarenal cross-clamp during juxtarenal or suprarenal repair.

In 69 patients who required a suprarenal cross-clamp, we found perioperative renal dysfunction and mortality to be 30% and 4%, respectively. Late renal dysfunction was documented in 17.5%, with 5-year intervention-free survival of 62% and overall survival of 77%. Crawford,[2] in 1986, reported a perioperative renal dysfunction rate of 16%, perioperative mortality of 7%, and 5-year survival of 75% in 101 patients who underwent a juxtarenal or suprarenal AAA repair. Other studies report similar results, although wide variation exists in renal dysfunction (8%-40%), mortality (<1%-12%), and 5-year survival

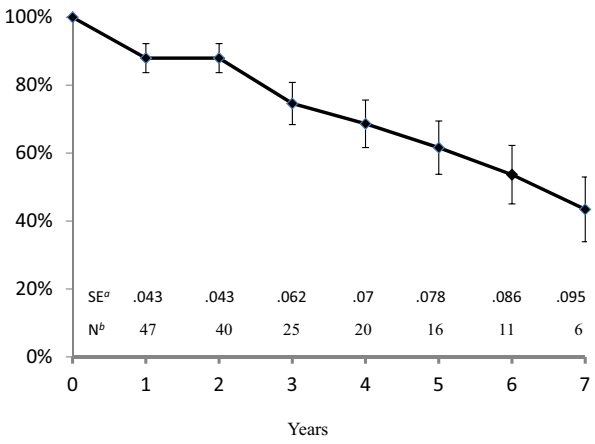

Fig 1. Intervention-free survival. *Error bars* show standard error (*SE*), which does not exceed 10% for each time interval. *N,* Effective sample size.

Table V. Univariate analysis of factors affecting intervention-free survival

	HR	P *value*
Age	1.05	.1
Race	1.17	.57
Hypertension	0.64	.43
Diabetes	1.12	.54
Hyperlipidemia	0.54	.15
CAD	1.05	.87
Preoperative sCr level	3.19	.34
Preoperative eGFR	1.6	.41
Statin	0.61	.28
Antiplatelet	.41	.04
Smoker, current or previous	1.37	.67
Cerebrovascular disease	0.95	.82
COPD	2.42	.09
Prior aortic surgery	3.43	.06
Transperitoneal approach	1.4	.59
Retroperitoneal approach	2.67	.1
Aneurysm location[a]	0.61	.47
Concomitant renal artery intervention[b]	0.6	.12
Hypotension		
Systolic BP <100 mm Hg	1.52	.76
Systolic BP <80 mm Hg	1.59	.28
Estimated blood loss		
>1 L	0.87	1
>2 L	1.31	.79
Transfusion	1.21	.8
Perioperative pneumonia	3.4	.12
Perioperative reintubation	0.68	.71
Perioperative renal dysfunction	0.4	.23
Perioperative arrhythmia	3.6	.06
Return to operating room	2.3	.19
Renal dysfunction at follow-up	0.68	.46

BP, Blood pressure; *CAD,* coronary artery disease, current or history; *COPD,* chronic obstructive pulmonary disease; *eGFR,* estimated glomerular filtration rate; *HR,* hazard ratio.
[a]Juxtarenal vs suprarenal.
[b]Renal artery bypass, reimplantation.

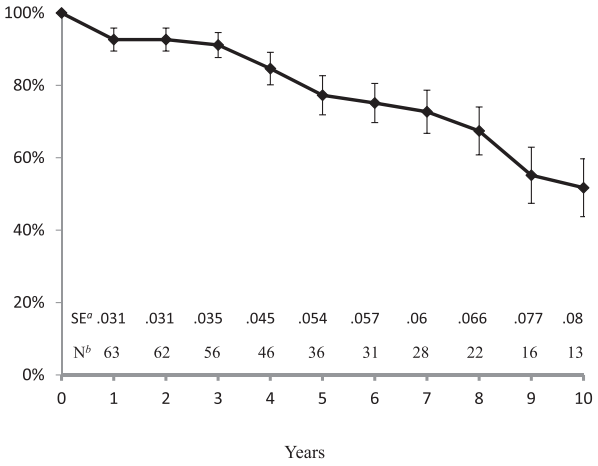

Fig 2. Overall survival. *Error bars* show standard error (*SE*), which does not exceed 10% for each time interval. *N,* Effective sample size.

(40%-75%).[1,3,5,6,15-19] Whereas the mortality rate for juxtarenal and suprarenal AAA repair was higher in earlier studies compared with infrarenal AAA repair,[3] more recent reports, including our own, document rates that have been reported for infrarenal AAA repair in prospective randomized EVAR trials.[1,4,15]

A confounding factor in analyzing and comparing renal dysfunction after suprarenal cross-clamping is that renal function is defined in disparate ways. To be consistent with more recent literature and to facilitate comparisons with current f-EVAR reports, we used percentage change in eGFR as our primary determinant. The eGFR was calculated by the MDRD study equation.[20] The MDRD formula is known to correlate well with actual changes in GFR.[20-22] Although this and other formulas for estimation have been shown to be imprecise in certain populations, they are clearly a more accurate reflection of renal function than sCr concentration alone, particularly in older patients with some level of preexisting renal dysfunction.

As was true in other reports, a significant postoperative decrease in eGFR was found to be an important factor in perioperative morbidity and mortality. However, defining clinical predictors of risk after suprarenal cross-clamping was elusive. Whereas requirement of any blood transfusion approached significance, increasing transfusion requirement, estimated blood loss, and systolic blood pressure were not significant. Pneumonia was found to be significant, but the association of early postoperative renal function decline with transfusion requirement and pneumonia is not clinically obvious. We surmise that both factors may be a marker for hemodynamic instability or aortic reconstruction complexity and associated with a longer operative time, which was found to have a significant impact on perioperative renal function.

The finding that preoperative renal function was not a predictor of early or late postoperative renal dysfunction is also interesting. This may be due to patient selection bias, which excluded most patients with significant preoperative renal dysfunction and thereby limited the power of statistical analysis. However, the importance of postoperative renal dysfunction on late renal function was clearly evident, with a significant late decline in eGFR found only in patients with postoperative renal dysfunction.

Few late interventions related to the AAA repair were required, and almost half were unrelated to the aortic reconstruction. Data in the literature on late intervention-free survival in open juxtarenal and suprarenal AAA repair are sparse; the majority of reports provide only the number or percentage of late complications or do not report on them at all. By inclusion of all reinterventions (both aortic and operation related), a more realistic and comparative assessment is given of intervention-free survival in the current endovascular environment.[23] The reason for the intervention-free survival benefit in patients receiving antiplatelet agents is unclear. However, because it did not affect overall survival, it may be an indicator of a positive effect on the durability of the aortic reconstruction. Further study will be required to answer if this is so.

Table VI. Univariate analysis of factors affecting survival

	HR	P *value*
Age	1.05	.09
Race	0.9	.67
Sex	0.78	.62
Hypertension	1.05	.93
Diabetes	1.19	.91
Hyperlipidemia	1.06	.15
CAD	1.4	.51
Preoperative sCr level	1.2	.86
Preoperative eGFR	1.6	.35
Statin	0.56	.18
Antiplatelet	0.49	.09
Smoker, current or previous	1.3	.67
Cerebrovascular disease	1.4	.54
COPD	3.7	.003
Prior aortic surgery	0.97	.94
Transperitoneal approach	0.4	.1
Retroperitoneal approach	2.59	.1
Aneurysm location[a]	1.25	.47
Concomitant renal artery intervention[b]	0.8	.37
Hypotension		
Systolic BP <100 mm Hg	1.04	1
Systolic BP <80 mm Hg	1.6	.28
Estimated blood loss		
>1 L	1.22	.77
>2 L	1.23	.79
Transfusion	1.67	.44
Perioperative pneumonia	7.2	.002
Perioperative reintubation	0.9	.84
Perioperative renal dysfunction	1.3	.6
Perioperative arrhythmia	1.84	.27
Return to operating room	2.27	.1
Renal dysfunction at follow-up	0.8	.6
Secondary intervention	1.3	.61

BP, Blood pressure; *CAD,* coronary artery disease, current or history; *COPD,* chronic obstructive pulmonary disease; *eGFR,* estimated glomerular filtration rate; *HR,* hazard ratio.
[a]Juxtarenal vs suprarenal.
[b]Renal artery bypass, reimplantation.

Overall late survival was favorable compared with previous studies.[1-3,15,16] It is well known that after aortic reconstruction, late survival is negatively affected by existing pulmonary disease, and our experience is no exception.[24-28] Chong et al[1] specifically looked at 5-year survival in patients requiring suprarenal cross-clamping and demonstrated that chronic obstructive pulmonary disease significantly decreased late survival. Surprisingly, we found late survival to not be influenced by preoperative, perioperative, or postoperative renal dysfunction.

Whereas our study specifically addresses open repair of juxtarenal and suprarenal AAAs, the current interest is its comparative effectiveness to f-EVAR. f-EVAR carries a risk of renal dysfunction, and that along with the need for reintervention remains a primary concern in both early and late outcomes.[7-13] A study by Kristmundsson[29] reported a 30-day mortality of 3.7% and perioperative renal dysfunction (defined as >30% rise in sCr concentration) in 35% of patients. Late renal function persisted in 16% at a mean follow-up of 25 months. A more recent report from the same patient cohort with a mean follow-up of 5.5 years found that 26% of patients with normal preoperative renal function and 22% of patients with preoperative renal dysfunction developed a >30% change in eGFR.[30] The 5-year intervention-free survival was 56%, and overall 5-year survival was 60%. In a recent review of eight studies on f-EVAR, average 30-day mortality was 1.7% (range, 0%-3.7%), renal dysfunction 11.4% (range, 0%-35%), hemodialysis requirement 1.9% (range, 0%-11.1%), and late mortality 15.1%, with a mean follow-up of 19.1 months (range, 0-87 months).[31]

CONCLUSIONS

Direct comparison of our study and others with the early results of f-EVAR is not possible, but this study and the collective literature provide guidance for application of f-EVAR absent a direct comparison through prospective randomized trials. Our findings indicate that about a quarter of patients who require a suprarenal cross-clamp during open juxtarenal or suprarenal AAA repair will experience renal dysfunction. However, although perioperative renal dysfunction is frequent, it has limited impact on intervention-free and overall patient survival. Intervention-free survival and overall survival are reasonable, given the comorbidities of this patient population, with pre-existing pulmonary disease being the main driver of late mortality. These findings provide additional guidance for patient selection in the fenestrated/branched graft era.

AUTHOR CONTRIBUTIONS

Conception and design: SW, KW, AY, FW
Analysis and interpretation: SW, KW, MS, SWH, VR, FW
Data collection: SW, AY, MS, SGH
Writing the article: SW, AY, FW
Critical revision of the article: SW, KW, MS, SGH, SWH, VR, FW
Final approval of the article: SW, KW, AY, MS, SGH, SWH, VR, FW
Statistical analysis: SW, KW
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